IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Behrooz Sharifi *et al.*
Application No. : 10/564,009
Filed : July 14, 2006
For : USE OF PLEIOTROPHIN IN THE DIAGNOSIS, TREATMENT AND PREVENTION OF DISEASE

Examiner : Kevin Kai Hill
Art Unit : 1633
Docket No. : 67789-080US0
Confirmation No.: 6133

DECLARATION OF RAMA NATARAJAN, PH.D.

I, Rama Natarajan, Ph.D., declare and state as follows:

1. I am currently a Professor at Gonda Diabetes Research Center, Beckman Research Institute of City of Hope.
2. I received my Master of Science degree in Chemistry from Bangalore University, India in 1973.
3. I received my Doctorate degree in Biochemistry from Indian Institute of Science, India in 1977.
4. Between 1977 and 1979, I was a Senior Research Fellow in the Department of Organic Chemistry at the Indian Institute of Science, Bangalore, India.
5. Between 1979 and1980, I was a Scientific Research Council Post Doctoral Fellow in the Department of Applied Chemistry at Salford University, England, U.K
6. Between 1980 and 1986, I was an NIH Post Doctoral Fellow in the Department of Medicine at the University of Southern California Medical School, Los Angeles, CA.

7. Between 1987 and 1990, I was an Assistant Professor in the Department of Medicine at the University of Southern California Medical School, Los Angeles, CA.

8. Between 1990 and 1996, I was an Assistant Research Scientist in the Division of Diabetes, Endocrinology & Metabolism at City of Hope, Duarte, CA.

9. Between 1996 and 2001, I was an Associate Professor in the Division of Diabetes, Endocrinology & Metabolism at City of Hope, Duarte, CA.

10. I have read U.S. Patent Application Serial No. 10/564,009 ("the '009 Application") and understand the contents of this patent application.

11. I understand that the pending claims of the '009 Application describe (1) methods of transdifferentiating a monocytic cell into an endothelial cell by artificially increasing the expression of pleiotrophin (PTN) in the monocytic cell by transducing the monocytic cell in vitro with a retrovirus expressing PTN such that the monocytic cell transdifferentiates into an endothelial cell; and (2) endothelial cells produced by these methods.

12. I understand the Examiner asserts the following:

    a. Patent Application Publication No. US 2002/0098166 (Havemann *et al.*) discloses PTN as a growth factor used in culturing monocytes to differentiate them into endothelial-like cells or endothelial progenitor cells.

    b. Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* would lead one of ordinary skill in the art to conclude that the gene to be expressed in the endothelial cells would reasonably refer to PTN.

    c. Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* would lead one of ordinary skill in the art to conclude that PTN may be used for inducing differentiation of monocytic cells into endothelial cells because PTN was allegedly recognized to be involved in growth and differentiation.

    d. Havemann *et al.* discloses the transfection of mononuclear cells with a nucleic acid construct for gene therapy, wherein the construct comprises an effector gene, the effector gene being a growth factor, and the growth factor being PTN.

e. The combined teachings of Havemann *et al.*, Souttou *et al.* and Powers *et al.* would lead one of ordinary skill in the art to believe that it would be predictable, and there would be a reasonable expectation of success, for a monocytic cell transduced with a retrovirus expressing PTN to transdifferentiate into an endothelial cell.

13. I have read and understand the disclosures of Havemann *et al.*, Souttou *et al.* and Powers *et al.*

14. Havemann *et al.* does not teach the use of PTN to differentiate monocytic cells into endothelial cells. Havemann *et al.* describes methods of culturing mononuclear cells under differentiation conditions of gangliosides, phospholipids, glycolipids and growth factors for endothelial cells. It is my opinion that skilled practitioners, such as myself, would not conclude that PTN can differentiate monocytic cells into endothelial cells based on the disclosures by Havemann *et al.* A general disclosure of culturing cells under differentiation conditions does not equate to a disclosure that PTN induces transdifferentiation of monocytic cells into endothelial cells.

15. It is my opinion that Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* would not lead skilled practitioners, such as myself, to transfect a monocytic cell with a retrovirus expressing a biologically active protein to transdifferentiate the monocytic cell into an endothelial cell. The combined disclosure would not lead me to believe that the gene to be expressed in the endothelial cells would reasonably refer to PTN.

16. It is my opinion that Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* would not lead skilled practitioners, such as myself, to conclude that PTN may be used for inducing differentiation of monocytic cells into endothelial cells.

17. I have read and understand the disclosures of Deuel *et al.* and Pufe *et al.* Deuel *et al.* notes that PTN has been recognized for differentiation of glial progenitor cells and as an angiogenic factor that promotes tumor angiogenesis. Pufe *et al.* notes that PTN can promote the replication of monocytes. However, these known properties of PTN do not suggest to skilled practitioners, such as myself, that PTN would induce differentiation of a monocytic cell into an endothelial cell.

18. It is my opinion that skilled practitioners, such as myself, would not view Havemann *et al.* as disclosing the transfection of mononuclear cells with a nucleic acid construct for gene therapy, wherein the construct comprises an effector gene, the effector gene being a growth factor, and the growth factor being PTN.

19. It is my opinion that the combined teachings of Havemann *et al.*, Soutou *et al.* and Powers *et al.* would not lead skilled practitioners, such as myself, to believe that it would be predictable, and there would be a reasonable expectation of success, for a monocytic cell transduced with a retrovirus expressing PTN to transdifferentiate into an endothelial cell.

20. I declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true, and further that these statement are made with the knowledge that willful false statements and the like are made punishable by fine, imprisonment, or both (18 U.S.C. §1001), and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: 7-15-10

Rama Natarajan, Ph.D.